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(54) PREPARATION OF CHROMONE-2-CARBOXYLIC ACIDS OR DERIVATIVES THEREOF

(71) We, FISONS PHARMACEUTICALS LIMITED, a British Company, of 12 Derby Road, Loughborough, Leicestershire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

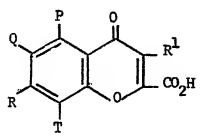
This invention relates to a novel process for preparing chromone-2-carboxylic acids and derivatives thereof.

According to our invention we provide a process for the production of a pharmaceutically acceptable derivative of a chromone-2-carboxylic acid, or a free chromone-2-carboxylic acid, which comprises cyclising a corresponding compound containing a benzene ring arrying in positions *ortho* to one another the substituents —OM and —COCHR^{1}COD wherein M represents a hydrogen or an alkali metal atom, R^1 represents hydrogen or an alkyl or aryl group containing from 1 to 10 carbon atoms, and D represents a —COOH group, or a group oxidisable or hydrolysable thereto, in an anhydous basic medium, working up the reaction product under non-acidic conditions, and, when a free chromone-2-carboxylic acid is required, oxidising or hydrolysing the group —D to a —COOH group.

The base used to provide the anhydrous basic medium may be an organic base, for example a tertiary organic base, such as pyridine or triethanolamine, and is preferably used in excess. The cyclisation may, if desired, be carried out in a solvent which is inert under the reaction conditions, for example dioxan, anisole or benzene; alternatively an excess of a suitable base may be used as solvent. The cyclisation is preferably carried out at an elevated temperature, for example at a temperature of from about 20°C to 120°C. The cyclisation should, of course, be carried out under conditions which do not cause opening of the chromone ring as it is formed.

The process of the invention may be applied to the formation of one, two or more chromone nuclei in the same compound. The formation of a plurality of chromone nuclei may take place in a single common cyclisation reaction or may take place in several stages.

According to a more limited form of our invention we provide a process for the production of a pharmaceutically acceptable derivative of a compound of formula I, (or a free compound of formula I)



I

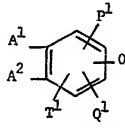
wherein R^1 is as defined above, and

P, Q, R and T, which may be the same or different, are each hydrogen; an alkyl group containing from 1 to 10 carbon atoms, a substituted alkyl group containing from

1 to 10 carbon atoms, an unsaturated alkyl group containing from 1 to 10 carbon atoms, an aralkyl or substituted aralkyl group wherein the alkyl group contains from 1 to 10 carbon atoms, a mono or polybenzenoid aryl, a substituted aryl, a heterocyclic, or a substituted heterocyclic group, a cycloalkyl group containing from 4 to 6 carbon atoms, a substituted cycloalkyl group containing from 4 to 6 carbon atoms, a nitrile, iminoether, amidine, nitro, nitroso, carboxylic acid, or hydroxy group, an alkoxy group containing 1 to 10 carbon atoms, a substituted alkoxy group, an unsaturated alkoxy group, an aralkyloxy, aryloxy or, a substituted aryloxy group, a hetero-oxy, cycloalkyloxy, epoxyalkoxy, amino, alkylamino, dialkylamino, carboxyamino, alkoxycarbonylamino, carboxy amide, cycloalkylamino, arylamino, diarylamino, haloalkylamino, alkenylamino, a halogen atom, an acyl group derived from one of the above alkyl or substituted alkyl groups, or an aldehyde group,

or an adjacent pair of P, Q, R and T may form a fused carbocyclic or heterocyclic ring, or may form a further pair of groups —OM and —COCHR^{1}COD, in which M, R^1 and D are as defined above, or

one of P, Q, R and T may be a group of formula III,

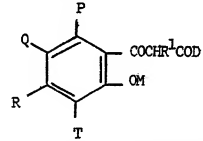


III

wherein P^1, Q^1 and T^1 have the same significance as P, Q and T save that they may not represent a group of formula III, and

A^1 and A^2 represents a chain —CO—CR^1=C(COOH)—O—, or a pair of groups —OM and —COCHR^{1}COD, or another pair of groups convertible to a chain —CO—CR^1=C(COOH)—O—, R^1, M and D being as defined above, and X represents a substituted or unsubstituted carbocyclic or heterocyclic ring or a branched or straight, saturated or unsaturated, substituted or unsubstituted hydrocarbon chain which chain may be interrupted by one or more carbonyl groups or oxygen atoms,

which process comprises cyclising a compound of formula II,

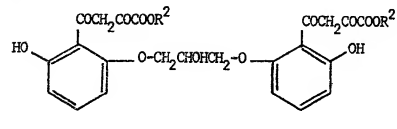


II

in which P, Q, R, T, R^1, D and M are as defined above,

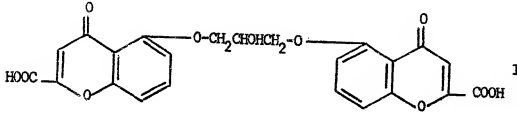
in an anhydrous basic medium, working up the reaction product under non-acidic conditions, and when a free compound of formula I is desired, oxidising or hydrolysing the group D to a —COOH group.

The process of this invention may be used to prepare the chromone-2-carboxylic acids described in our published Dutch Applications Nos. 66,03997 and 68,11740. In particular the process of this invention may be used to convert a compound of formula IIa,



IIa

in which R^2 represents an alkyl group containing from 1 to 10 carbon atoms, to a salt or a C1 to 10 alkyl ester of a compound of formula Ia,



Ia

Preferred values of P, Q, R, T, P^1, Q^1 and T^1 are hydrogen, halogen, hydroxy, carboxy, alkoxycarbonyl, nitro, alkyl, alkenyl, alkynyl, aralkyl, aryl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, aralkoxy or acyl groups or the fused ring substituents specified above, or these groups carrying substituents, such as halogen, hydroxy or alkoxy groups. Particularly preferred compounds are those carrying hydrogen or halogen (especially chlorine or bromine), nitro and lower alkyl, alkenyl, alkoxy or alkenyloxy goups containing from 1 to 6 carbon atoms which may carry one or more hydroxy, lower alkoxy or aryl substituents.

It is preferred that R^1 should be hydrogen.

It will be appreciated that certain of the above values of P, Q, R and T include groups which might be detrimentally affected by the reactants and/or reaction conditions used during the processes of the invention. In such cases the affected group or site may be blocked or shielded as necessary.

The compounds used as starting materials for our process, e.g. the compounds of formula II, are either known or may be made by methods analogous to those known for the manufacture of the known compounds. In certain cases the compounds of formula II need not be isolated from the reaction mixture in which they are formed and indeed the reaction mixture may be such as to cause their cyclisation as soon as they are formed.

The groups —D may be those known to be oxidisable or hydrolysable to a —COOH group, and may be for example an ester, a methyl or a styryl group, and the conversion of the —D group to a —COOH group may be carried out using conventional techniques.

The product of the process of the invention may be recovered from the reaction mixture in which it was prepared and may be purified using conventional techniques which do not involve the use of acidic conditions. It is also within the scope of the present invention to treat the product, which may exist in a number of forms, e.g. as a salt or ester of the carboxylic acid function thereof or as the free acid depending upon the method used to obtain the product, further to convert them into a more desired form. This further treatment may be carried out using conventional techniques. Thus, salts may be prepared by the use of alkaline conditions during the recovery and purification of the compound. Alternatively, the free acid may be obtained and subsequently converted to a desired salt by neutralisation with an appropriate base, e.g. an organic amine, or alkali such as an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate, preferably a mild base or alkali such as sodium carbonate or bicarbonate. Where the compound is recovered in the form of a salt this salt may be converted to a more desirable salt, for example by a metathetical process. The esters may be obtained as a resulting of having used appropriate starting materials, or may be formed by the reaction of an appropriate alcohol, alkyl sulphate or halocompound with free carboxyl groups in the compound. Alternatively transesterification techniques may be used to exchange one ester group for another. The amides may be readily obtained, for example, by dehydration of the ammonium salt or by reaction of the free carboxyl groups in the compound with an appropriate amino compound such as a primary or secondary alkyl or aryl amine or an amino acid. The free acids may also be condensed with an amino acid or ester in the presence of an alkyl haloformate (e.g. ethyl chloroformate) an an organic base (e.g. triethylamine) together with a mineral alkali (e.g. sodium hydroxide) in a suitable solvent to give an N-carboxyalkyl substituted amine.

The chromone-2-carboxylic acids, and pharmaceptically acceptable derivatives thereof, are useful because they possess pharmacological properties. They are indicated for use in the treatment of allergic asthma.

Our invention has the advantage that the process does not involve an acid treatment to cause cyclisation, a step which had previously been considered as necessary to such cyclisation.

The process of the invention will be illustrated by the following Examples in which all parts are given by weight unless otherwise stated:

Example 1

2-Ethoxycarbonyl-7-hydroxy-3-phenylchromone

A solution of 16.2 parts of 2,4-dihydroxyphenyl benzylketone in 160 parts of dry pyridine was cooled in an ice-bath and then treated dropwise with 35.2 parts of ethoxalyl chloride with stirring to form 2,4-dihydroxyphenyl-ω-ethoxalyl-ω-benzyl-ketone (not isolated). After the addition, the mixture as allowed to reach room temperature and then heated on a steam bath for 2 hours.

The solution was cooled, then poured into water and extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulphate, filtered and evaporated to dryness to leave a brown oil. This oil was extracted with diethyl ether. The ethereal solution was concentrated to give 5.85 parts of 2-ethoxycarbonyl-7-hydroxy-3-phenylchromone as fawn needles, melting point 208—11°C.

Example 2

Diethyl ester of 1,3-bis (2-carboxychromon-5-yloxy)-2-hydroxypropane

(a) 1,3-Bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane

A mixture of 10 parts 2,6-dihydroxyacetophenone, 7.15 parts of 1,3-dibromopropan-2-ol and 4.6 parts powdered potassium carbonate were heated under reflux in 200 parts by volume of acetone for 72 hours. The acetone solution was filtered and the solid residue was washed first with acetone and then with water. The combined acetone filtrate and washing were evaporated leaving an oil which, on being boiled with ether, gave pale yellow crystals. These were combined with the first obtained solid and extracted with refluxing isopropanol in a Soxhlet extractor for several days to obtain 3 parts of 1,3-bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane as almost colourless crystals melting between 184° and 185°C.

Analysis:

Found: C, 63.5; H, 5.86%
$C_{19}H_{20}O_7$ requires: C, 63.3; H, 5.56%

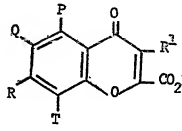
(b) Diethyl ester of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane

A solution of 10 parts of 1,3-bis(2-aceyl-3-hydroxyphenoxy)-2-hydroxypropane in 100 parts of dry pyridine was treated dropwise with 25 parts of ethoxalyl chloride at 0 to 5°C to yield 1,3-bis(2-ethoxalylacetyl-3-hydroxyphenoxy)-2-hydroxypropane (not isolated). The mixture was stirred and allowed to reach room temperature. It was then heated on the steam bath for 3 hours. After cooling, the mixture was poured into water and extracted with chloroform. After drying the chloroform extracts, the solvent was removed and the residue was crystallised from a benzene-petroleum mixture to give the diethyl ester of 1,3 bis(2-carboxychromon-5-yloxy) 2-hydroxypropane m.pt. 180—182°C.

WHAT WE CLAIM IS:—

1. A process for the production of a pharmaceutically acceptable derivative of a chromone-2-carboxylic acid, or a free chromone-2-carboxylic acid, which comprises cyclising a corresponding compound containing a benzene ring carrying in positions *ortho* to one another the substituents —OM and —COCHR'COD wherein M represents a hydrogen or an alkali metal atom, R' represents hydrogen or an alkyl or aryl group containing from 1 to 10 carbon atoms, and D represents a —COOH group, or a group oxidisable or hydrolysable thereto, in an anhydrous basic medium, working up the reaction product under non-acidic conditions, and, when a free chromone-2-carboxylic acid is required, oxidising or hydrolysing the group —D to a —COOH group.

2. A process according to Claim 1, which comprises producing a pharmaceutically acceptable derivative of a compound of formula I, (or a free compound of formula I)



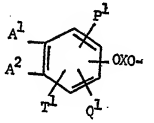
I

wherein R^1 is as defined in Claim 1 and

P, Q, R and T, which may be the same or different, are each hydrogen; an alkyl group containing from 1 to 10 carbon atoms, a substituted alkyl group containing from 1 to 10 carbon atoms, an unsaturated alkyl group containing from 1 to 10 carbon atoms, an aralkyl or substituted aralkyl group wherein the alkyl group contains from 1 to 10 carbon atoms, a mono or polybenzenoid aryl, a substituted aryl, a heterocyclic or a substituted heterocyclic group, a cycloalkyl group containing from 4 to 6 carbon atoms, a substituted cycloalkyl group containing from 4 to 6 carbon atoms, a nitrile, iminoether, amidine, nitro, nitroso, carboxylic acid, or hydroxy group, an alkoxy group containing 1 to 10 carbon atoms, a substituted alkoxy group, an unsaturated alkoxy group, an aralkyloxy, aryloxy or, a substituted aryloxy group, hetero-oxy, cycloalkyloxy, epoxyalkoxy, amino, alkylamino, dialkylamino, carboxyamino, alkoxycarbonylamino, carboxy amide, cycloalkylamino, arylamino, diarylamino, haloalkylamino, alkenylamino, a halogen atom, an acyl group derived from one of the above alkyl or substituted alkyl groups, or an aldehyde group,

or an adjacent pair of P, Q, R and T may form a fused carbocyclic or heterocyclic ring, or may form a further pair of groups —OM and —$COCHR^1COD$, in which M, R^1 and D are as defined in claim 1, or

one of P, Q, R, and T may be a group of formula III,

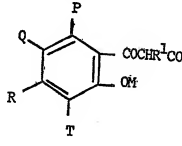


III

wherein P^1, Q^1 and T^1 have the same significance as P, Q and T save that they may not represent a group of formula III, and

A^1 and A^2 represent a chain —CO—CR^1=C(COOH)—O—, or a pair of groups —OM and —$COCHR^1COD$, or another pair of groups convertible to a chain —CO—CR^1=C(COOH)—O—, R^1, M and D being as defined in claim 1, and X represents a substituted or unsubstituted carbocylic or heterocyclic ring or a branched or straight, saturated or unsaturated, substituted or unsubstituted hydrocabon chain which chain may be inerrupted by one or more carbonyl groups or oxygen atoms,

which process comprises cyclising a compound of formula II,



II

in which P, Q, R, T, R^1, D and M are as defined above,

in an anhydrous basic medium, working up the reaction product under non-acidic conditions, and where a free compound of formula I is required, oxidising or hydrolysing the group D to a —COOH group.

3. A process according to either of Claims 1 or 2, wherein the anhydrous basic medium comprises a tertiary organic base.

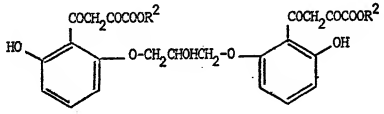
4. A process according to any of the preceding claims, wherein the anhydrous basic medium comprises pyridine.

5. A process according to any of the preceding claims, wherein the cyclisation is carried out in an inert organic solvent.

6. A process according to any of Claims 1 to 4, wherein the cyclisation is carried out using an excess of a suitable base as solvent.

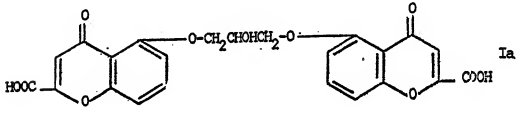
7. A process according to any of the preceding claims whenever applied to the formation of two chromone nuclei in the same compound in a single common cyclisation reaction.

8. A process according to any of the preceding claims, which comprises cyclising a compound of formula IIa,



IIa

in which R^2 represents an alkyl group containing from 1 to 10 carbon atoms, to form a salt or an alkyl C1 to 10 ester of compound of formula Ia,



Ia

9. A process according to any of Claims 2 to 7, wherein P, Q, R, T, P^1, Q^1 and T^1, which may be the same or different, are hydrogen, halogen, hydroxy, carboxy, alkoxycarbonyl, nitro, alkyl, alkenyl, alkynyl, aralkyl, aryl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, aralkoxy or acyl groups or the fused ring substituents specified in Caim 2, or these groups carrying substituents, such as halogen, hydroxy or alkoxy groups.

10. A process according to Claim 9, wherein P, Q, R, T, P^1, Q^1, and T^1, which may be the same or different, are hydrogen, chlorine, bromine, a nitro or lower alkyl, alkenyl, alkoxy or alkenyloxy group containing from 1 to 6 carbon atoms which may carry one or more hydroxy, lower alkoxy or aryl substituents.

11. A process according to any of the preceding claims, wherein R^2 is hydrogen.

12. A process according to any of the preceding claims, wherein the chromone-2-carboxylic acid produced is converted to a pharmaceutically acceptable derivative thereof.

13. A process for the production of a chromone-2-carboxylic acid, or a pharmaceutically acceptable derivative thereof, substantially as hereinbefore described.

14. A process for the production of a chromone-2-carboxylic acid, or a pharmaceutically acceptable derivative thereof, substantially as hereinbefore described in either of Examples 1 or 2.

15. A chromone-2-carboxylic acid, or a pharmaceutically acceptable derivative thereof, whenever prepared by a process claimed in any of the preceding claims.

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